Rare Finding of Bilateral Pseudoangiomatous Stromal Hyperplasia of the Breast: A Case Report

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A 49-year-old woman, with a medical history of rheumatism, was admitted to our hospital with chief complaints of bilateral enlargement and redness of breasts. She underwent weekly breast examinations. Mammography findings were reported as category 3 for both breasts. Breast ultrasonography, magnetic resonance imaging, and chest contrast computed tomography revealed a massive tumor in the left BD region, however, there were no findings for suspected malignancy. Needle biopsy did not yield histologically malignant cells in both breasts. Mammary interstitium was edematous, and capillary-like slit structures were observed. The stroma stained with alcian blue and destained with hyaluronidase treatment. Since the stroma tested positive for vimentin, calponin, and CD34 and negative for CD31, the patient was diagnosed as (PASH). Because both breasts had similar diagnosis based on histopathologic findings, bilateral mastectomy was performed. Details about the origin of bilateral PASH are unknown but it may be related to the development of rheumatoid arthritis. Additionally, systemic autoimmune diseases like rheumatism may be the reason for repeated contraction and enlargement of PASH.

Key words: Nodular pseudoangiomatous stromal hyperplasia of the breast (PASH), breast cancer, vimentin, mammography

INTRODUCTION

Pseudoangiomatous stromal hyperplasia (PASH) is a benign disease that exhibits marked hyperplasia of the mammary stroma, but rarely shows tumor formation and diffused theme. It is often reported to be localized in a part of the stroma of mammary gland. In this report, we describe a case of bilateral PASH that exacerbated repeatedly with marked mass formation.

CASE PRESENTATION

A 49-year-old woman noticed bilateral swelling and redness of her breasts. Although the sizes of the breasts fluctuated as noted during weekly follow-up visits, her symptoms gradually worsened. Mammography (MMG), ultrasound, and magnetic resonance imaging (MRI) examinations done at a previous doctor's office had revealed a high-density tumor shadow in the left BD area, the entire right region, and it was diagnosed as bilateral category 3 in the MMG examination (Fig. 1). MRI had revealed numerous tumors that densely packed on both sides (Fig. 2); they were diagnosed as lamellar tumors, and samples were sent to our hospital for further examination.

Although her family history was unremarkable, the patient had a medical history of rheumatoid arthritis, diagnosed a year ago, for which she was taking bucillamine and methotrexate.

Physical examination records of the patient at our hospital were as follows: height, 148 cm; weight, 51 kg; body temperature, 36.5˚C; pulse rate, 80 beats/min; arterial blood pressure, 118/64 mmHg; and no anemia or jaundice. Both breasts showed redness and had swollen to a size of a soccer ball (Fig. 3).

Breast ultrasonography revealed a lot of low-intensity echoes in the mammary gland tissue which were very heterogeneous. In addition, skin thickening around the redness was conspicuous, 6 mm on the right (Fig. 4a) and 5 mm on the left (Fig. 4d). Subcutaneous fat layer was thin. Based on the above observations, bilateral breast edema of the skin and subcutaneous fat was suspected. In addition, the giant tumor in the left EDB area was 148 × 112 mm in size, resembled a phyllodes tumor, with a smooth tumor border and internal echo concentration was homogeneous. The posterior echo was reinforced and speculated to be a soft lesion in the dynamic taste. Sliding of the large pectoral muscle was deep and could not be evaluated. Although the possibility of lamellar tumor could not be denied, considering that it was a uniform, soft lesion on the whole, the possibility of a benign proliferative lesion was considered (Fig. 4).

Needle biopsy was performed to obtain definite diagnosis. It was a tissue in both ducts originating

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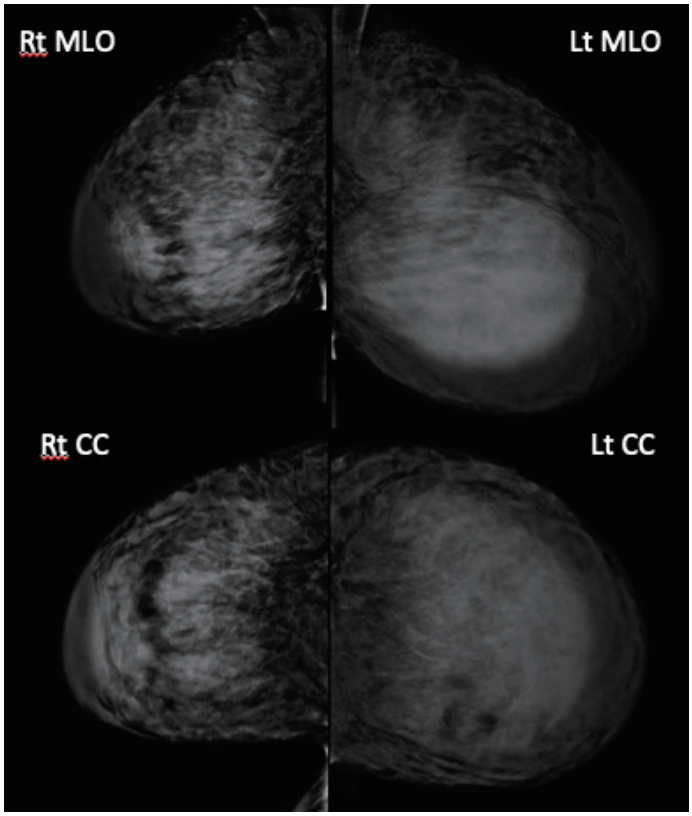

Fig. 1 Mammography results after first visit. In the right breast, thickening of the skin in the E region is observed especially in CC. In the left breast, an equi-density tumor is seen with a large clear boundary around the BD region and a smooth surface.

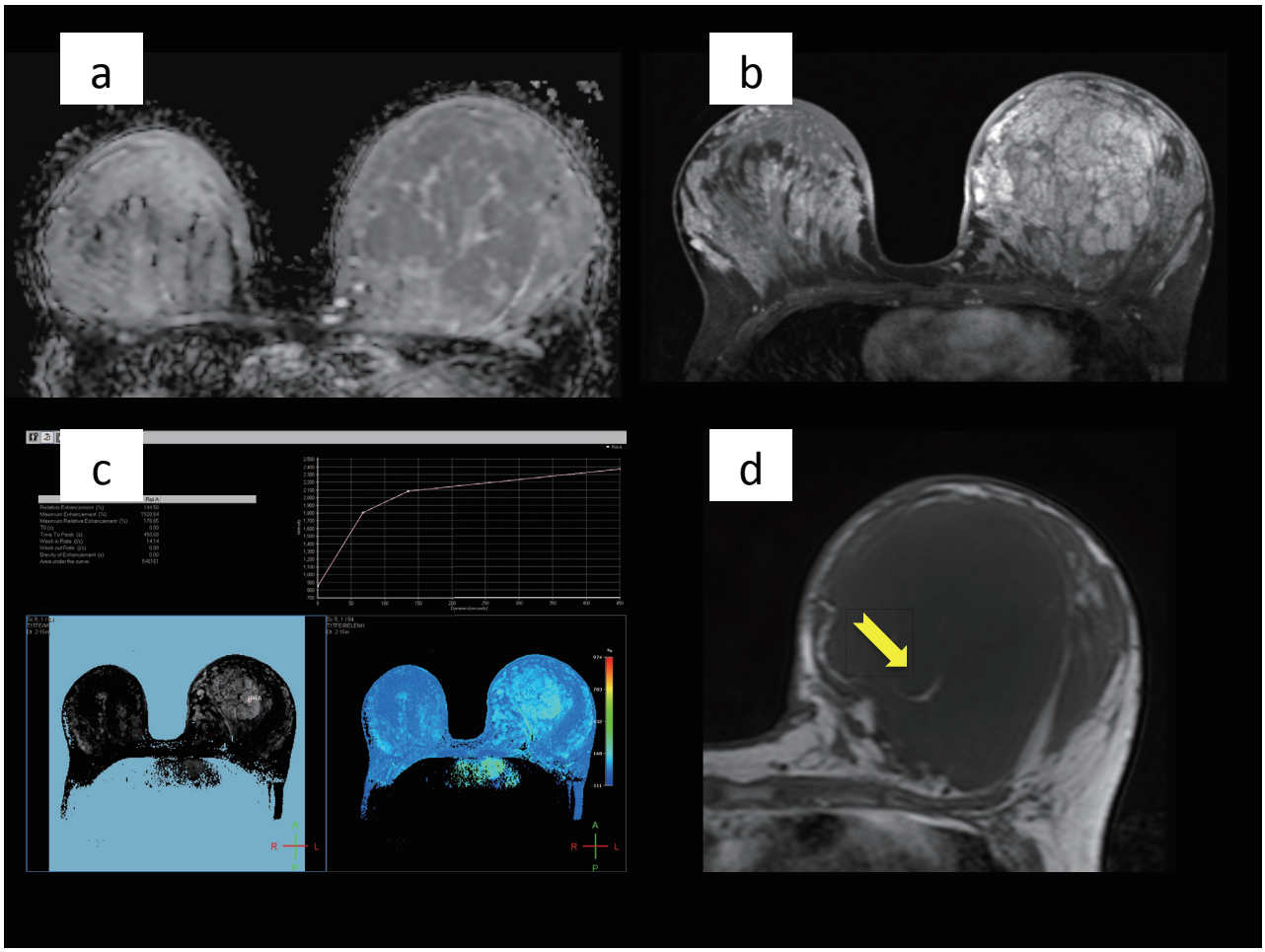

Fig. 2 Magnetic resonance imaging (MRI) examination. (a) dynamic MRI imaging, (b) T2W1, (c) Blood flow data during dynamic imaging, (d) T2W1, a fat formula within the tumor (yellow arrow).

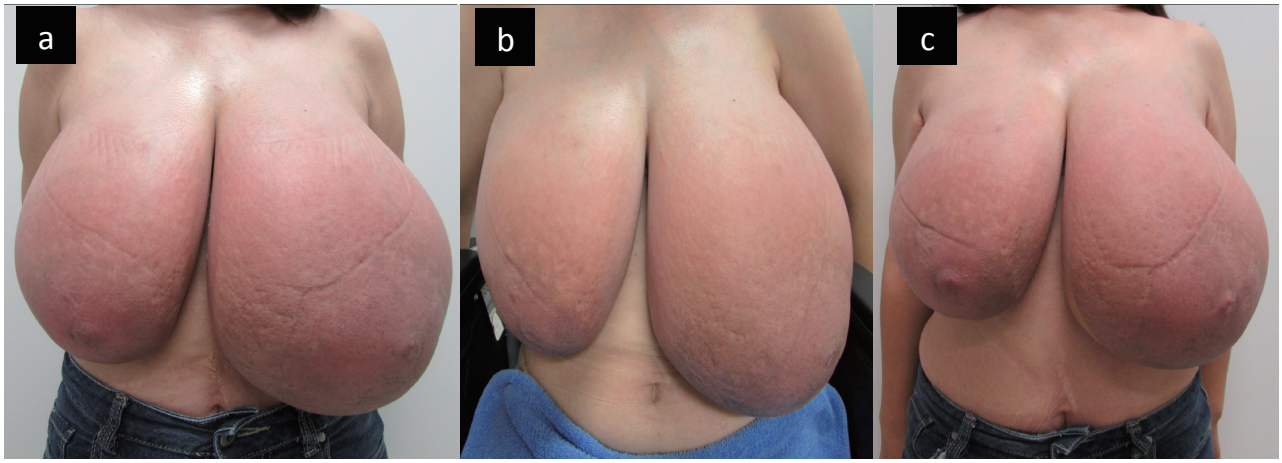

Fig. 3 Changes over time on visual inspection. (a) First visit, (b) 9 days, (c) 17 days.

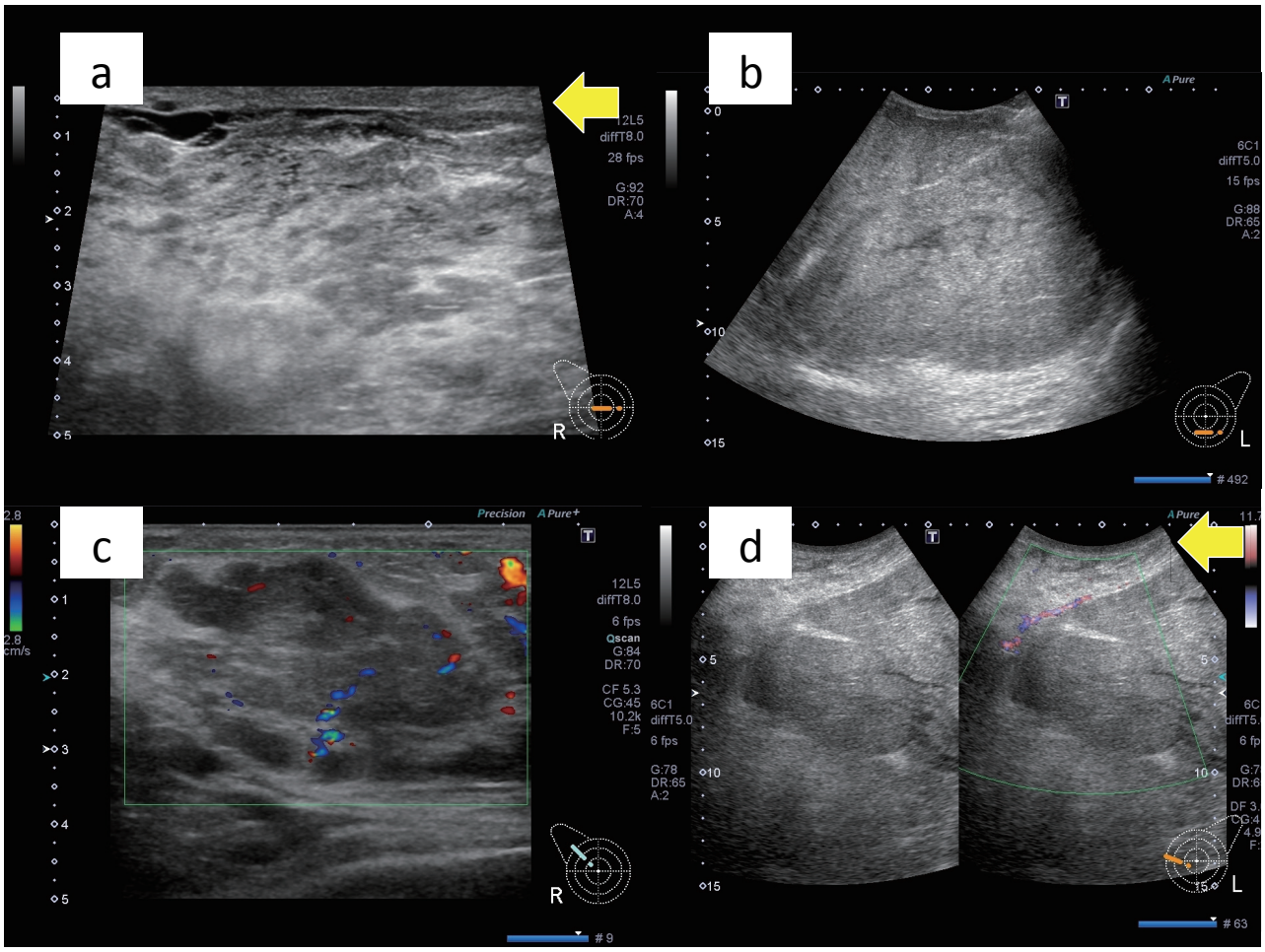

Fig. 4 Breast ultrasound examination at first visit. (a) right breast E region. Skin thickening is seen (yellow arrow). (b) left breast BD area. (c) blood flow Doppler echo of the right breast. (d) blood flow Doppler echo of the giant mass in the left breast. Skin thickening is seen (yellow arrow).

from interstitial stroma fibroids and maintained in the two-layer structure. Since fibroadenoma or foliate tumor was ruled out, additional staining was performed. The mammary interstitium was edematous, and a capillary-like slit structure was found in many places. The stroma stained with alcian blue (pH 2.5) but destained after hyaluronidase treatment. Spindle-shaped cells bordering the slit-structures were negative for vimentin, calponin, cytokeratin (AE 1/3), desmin, CD31, and factor-8, and positive for CD34 in immunohistochemical staining. Based on the above results, PASH was strongly suspected (Fig. 5).

Computerized Tomography (CT)

Computerized tomography of both breasts — that were enlarged and accompanied by skin thickening — suggested PASH. In addition, an elliptical mass of 15 cm was found in the BD region of left breast further indicating PASH (Fig. 6).

The left axillary lymph node was enlarged but seemed to be reacting to swelling. Other abnormalities were not evident.

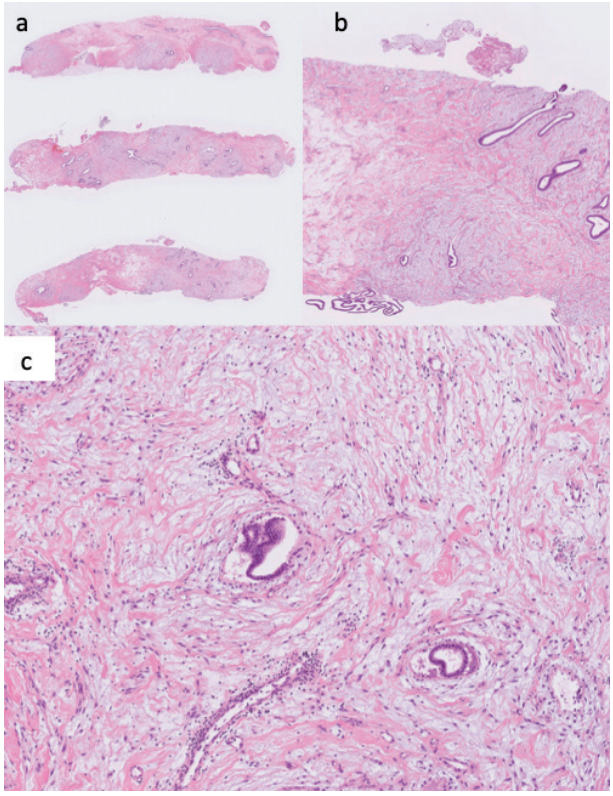

Fig. 5 Histopathological examination of needle biopsy by HE staining, (a) weak expansion, (b) medium expansion, (c) strong expansion.

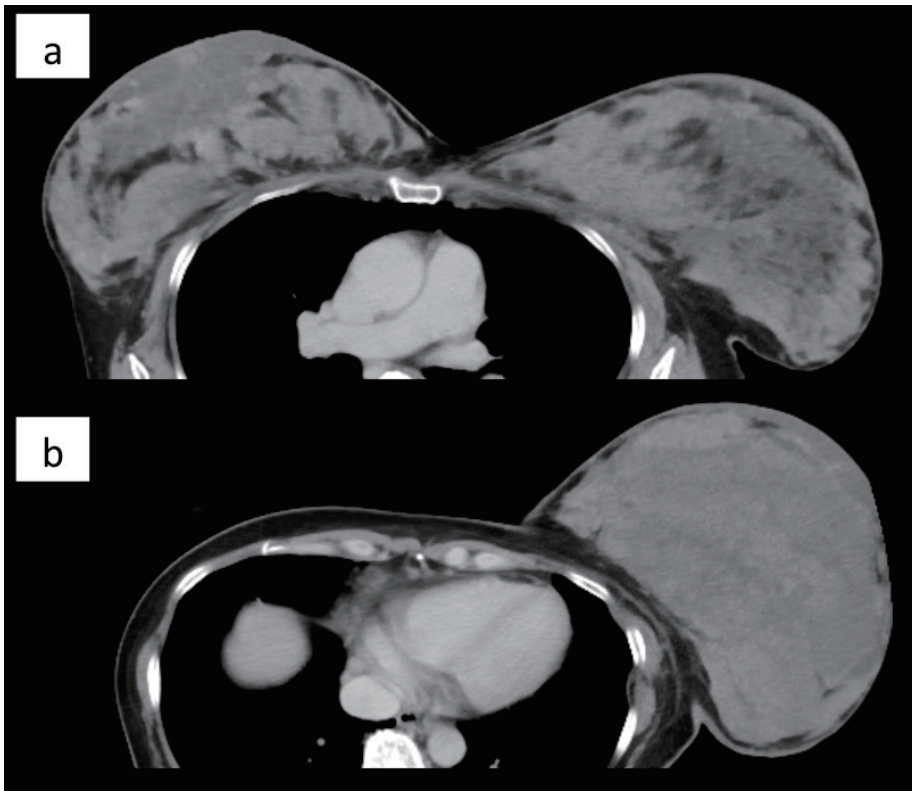

Fig. 6 Contrast-enhanced CT examination. (a) Coronary disconnection of the bilateral breast. (b) Tumor area of the left breast.

Surgery

From the above observations, PASH was strongly suspected. Although malignancy was not confirmed, the massive tumor (Fig. 7) repeatedly shrunk and enlarged over time deteriorating the patient's quality of life drastically. Hence, after adequately informing the patient about her condition, we performed a bilateral mastectomy.

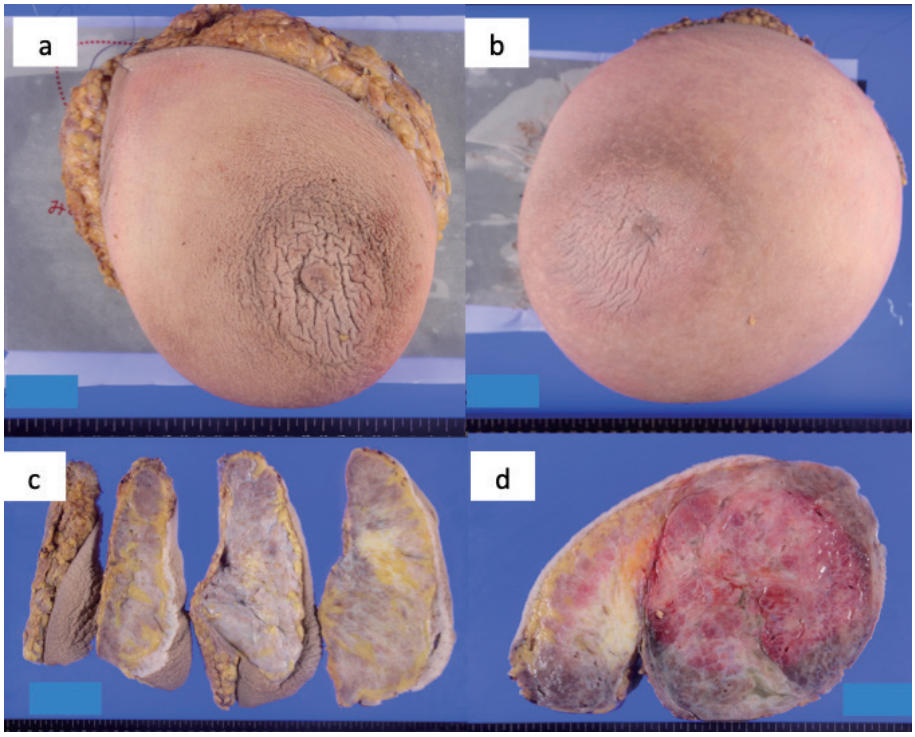

Fig. 7 Macro image of specimen resected during surgery. (a) right breast, (b) left breast, (c) sectional view of right breast, (d) sectional view of the left breast.

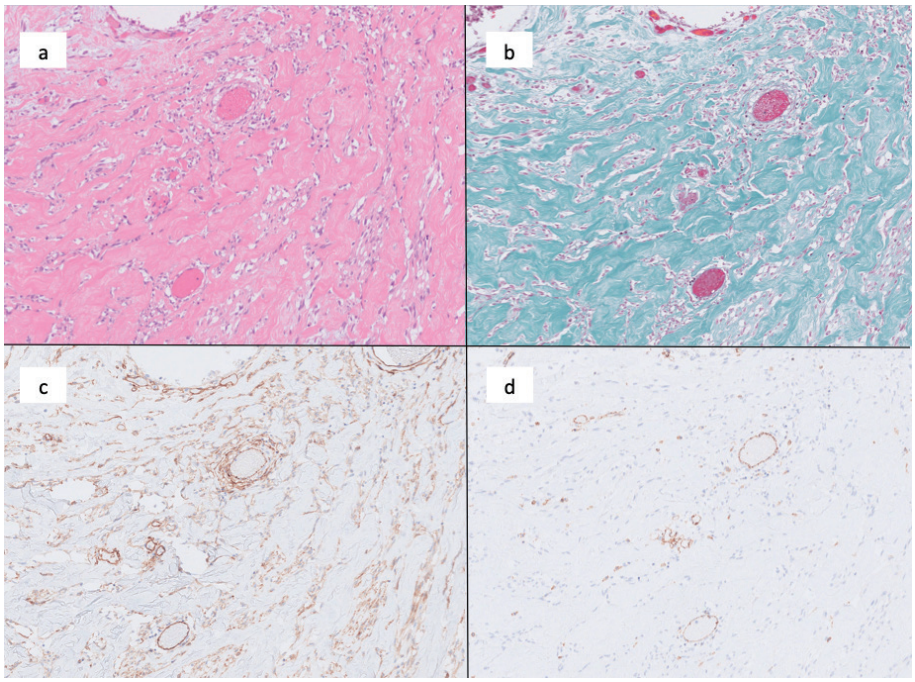

Fig. 8 Immunohistological staining of surgically resected specimens. (a) HE staining, (b) E-masson staining, (c) CD 34 staining, (d) CD31 staining.

Pathological findings

During surgery, a lobular mass with a relatively clear boundary was observed. A diffuse duct was found in the tumor area, and a capillary-like slit structure was observed in the stroma. The stroma stained with alcian blue (pH 2.5), but destained after hyaluronidase treatment. Spindle-shaped cells bordering the slits were negative for vimentin, calponin, cytokeratin (AE1/3), desmin, CD31, and factor-8 and positive for CD34 in immunohistochemical staining. Breast ducts maintained a two-layer structure and proliferative changes were not noticeable. An edematous change of the mammary interstitium was seen in the mammary gland tissue, which was not found to be a tumor or a mass. Lesions did not extend to the skin/dermis (Fig. 8). Surgical margins were negative.

The final pathological diagnosis was PASH on both sides.

DISCUSSION

PASH was first reported by Vuitch *et al.* in 1986 [1]. It is a hyperplastic lesion characterized by the formation of mammary gland lacquer and a gap between the lumen of the vessel, occasionally forming a tumor

Table 1 Laboratory findings at admission

WBC	6200	/ul	TP	7.8	g/dl	CRP	0.8	< 0.3	mg/dl
RBC	4.15	10^6/ul	Alb	3.7	g/dl	HbA1c	5.8	4.6 - 6.2	%
Hb	11.3	g/dl	GOT	30	U/L	IgG	1993	870 - 1300	mg/dl
Ht	36.5	%	GPT	18	U/L	IgA	132	110 - 350	mg/dl
PLT	37.3	10^4/ul	ALP	249	U/L	IgM	170	30 - 180	mg/dl
			Cr	0.74	mg/dl	IgE	19	< 500	IU/ml
			BUN	9	mg/dl	CEA	2.7	< 5.0	ng/ml
			Glu	88	mg/dl	CA15-3	32.9	< 30	U/ml
			Na	140	mEq/L	IgG-4	61.8	4.5 - 117	mg/dl
			K	4.3	mEq/L	CH50	33.4	25.0 - 48.0	
			Cl	105	mEq/L	RF	223	< 20	IU/ml
			Ca	8.8	mg/dl	α-SS-A	(-)	(-)	
						α-SS-B	(-)	(-)	
						α-CCP	> 500	< 4.5	U/ml
						IL-2R	850	145-519	U/ml

mass [2]. Mainly, PASH is regarded as one of pathological findings, though it rarely leads to formation of a mass. Further, there are reports that it merges with various mammary interstitia, such as hamartoma and gynecomastia [3]. PASH is more common in premenopausal women, but it also affects postmenopausal women on hormonal adjuvant therapy and is also known to often accompany the stromal tissue in male gynecomastia. The hematoxylin-eosin (HE) histopathology of the stroma is similar to that of normal luteal breast stroma and is often positive for progesterone receptor, hence it is considered to be a stromal response to progesterone. However, since spontaneous disappearance of stromal tissue has been reported, it is desirable to diagnose such tissue by biopsy and careful follow-up through image analysis as suggested by other reports. In this case, the patient was postmenopausal, and surgery seemed to be the best treatment option, given that her hormonal balance was unlikely to change significantly in the future.

Although the etiology of PASH is unknown, the possibility of proliferative response of myofibroblasts by hormone stimulation is considered and while it has been reported to occur more frequently in women using oral contraceptives or postmenopausal hormone replacement therapy, it did not apply to this case.

Mass formation in PASH is commonly found as a tumor of 3 to 5 cm which gradually increases, but in this case both breasts were huge, more than 10 cm each, although repeated increase or decrease in size has been rarely reported. In addition, bilateral PASH is atypical. However, bilateral PASH in our patient with concurrent expansion and contraction, suggested the involvement of certain systemic factors. Given the patient's medical history, it is possible that rheumatism may be the affecting factor.

Imaging results are often similar to fibroadenoma and lamellar tumor, while in ultrasound, it is visualized as a tumor with a clear boundary and internal nonuniformity.

As seen in pathological findings, tumorigenic PASH in general forms an elastic, hard gray-white to yellowish-white solid tumor mass with a smooth surface and no coating, but occasionally occur with a film or as a cyst. Some involve the surrounding structure. Histologically, along with the increase in mammary interstitium, slit-like gaps lined with spiked cells with poor heterotypes show irregular anastomoses with intervening ducts and lobules. In the interstitial cells in the duct epithelium, there were no cell heterotypes or mitotic figures. The breast ducts show changes in epithelium, myoepithelial hyperplasia and gynaecomastia-like appearance, and in this case as well, ductal epithelium and hyperplasia of myoepithelium were observed. Immunohistologically, interstitial spindle-shaped cells are negative for endothelial cell markers like factor VIII and CD31.

On the other hand, it has been reported that spindle-shaped cells are positive for the myofibroblast marker αSMA and desmin. Some are even positive for hormone receptors, especially progesterone receptors. In diagnostic imaging, low-grade angiosarcoma and fibroadenoma, myofibroblastoma, hamartoma, etc. are mentioned as differential diagnosis, but all can be distinguished based on morphological and immunohistochemical features.

Pseudoangiomatous stromal hyperplasia is rarely malignant, and although tumor resection is sufficient, there have been reports of local recurrence of PASH at a frequency of 12.5% to 29% if insufficient resection occurs [4, 5].

Herein, we report a rare case of PASH of bilateral breasts. The details of the origin of bilateral PASH are unknown. However, based on the simultaneous occurrence of rheumatoid arthritis, we speculated that the systemic autoimmune disease, rheumatism, may be related to the repeated contraction and enlargement of PASH, likely generated as a host immune response.

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REFERENCES

1) Vuitch MF, Rosen PP, Erlandson RA. Pseudoangiomatous hyperplasia of mammary stroma. Hum Pathol 1986; 17: 185-91.
2) Ibrahim RE, Sciotto CG, Weidner N. Pseudoangiomatous hy-

perplasia of mammary stroma. Some observations regarding its clinicopathologic spectrum. Cancer 1989; 63: 1154–60.
3) Milanezi MF, Saggioro FP, Zanati SG, Bazan R, Schmitt FC. Pseudoangiomatous hyperplasia of mammary stroma associated with gynaecomastia. J Clin Pathol 1998; 51: 204–6.
4) Nassar H, Elieff MP, Kronz JD, Argani P. Pseudoangiomatous stromal hyperplasia (PASH) of the breast with foci of morphologic malignancy: a case of PASH with malignant transformation? Int J Surg Pathol 2010; 18: 564–9.
5) Goel NB, Knight TE, Pandey S, Riddick-Young M, de Paredes ES, Trivedi A. Fibrous lesions of the breast: imaging-pathologic correlation. Radiographics 2005; 25: 1547–59.